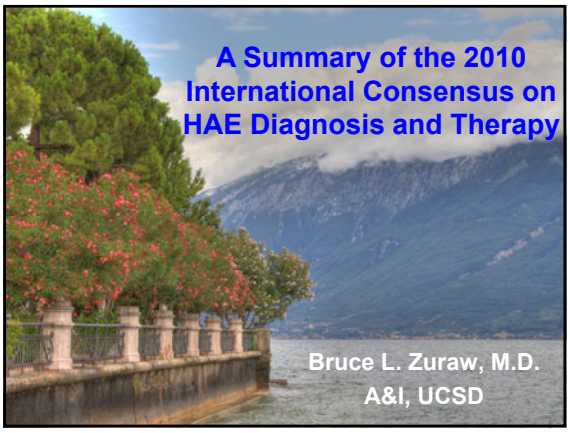


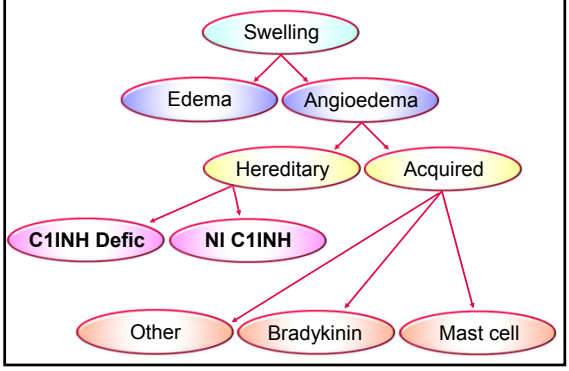
Disclosures

- *Consultant, Advisory Board*
  - *Dyax*
  - *Shire*
  - *BioCryst*
- *Speaker*
  - *Dyax*
  - *Santarus*
- *Honorarium*
  - *Dyax*
  - *Shire*
  - *Santarus*
  - *BioCryst*
- *Research Grant*
  - *Shire*
  - *Pharming*

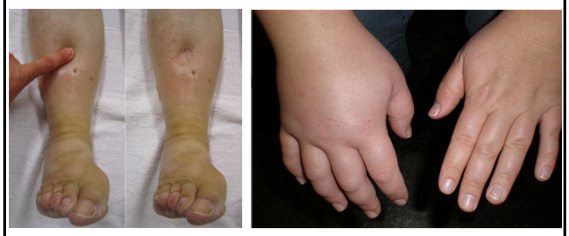
Learning Objectives

- ***At the conclusion of this session, participants should be able to:***
  - Evaluate whether a patient with recurrent angioedema suffers from hereditary angioedema
  - Develop a treatment plan for patients with hereditary angioedema based on current consensus guidelines

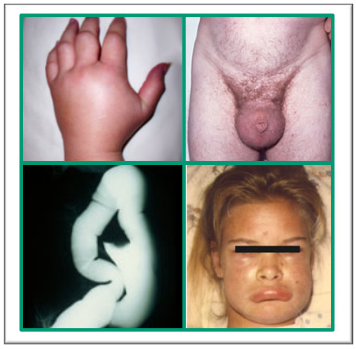
Giant Swelling



Angioedema versus Edema



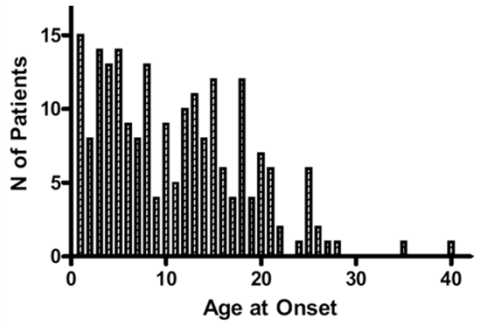
HAE Most Frequent Attack Locations



Diagnostic Clues for HAE

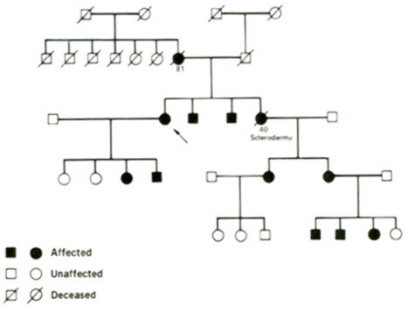
- Angioedema without urticaria
- Attacks may be preceded by prodromal symptoms
- Angioedema often quite severe
- Attacks are prolonged, typically 72-96 hrs
- Swelling is unresponsive to therapy with antihistamines, corticosteroids, or epinephrine
- Attacks may be precipitated by estrogens, trauma, or stress
- Family history of angioedema in most patients

Age at Onset of HAE Attacks



Bork K, et al. *Am J Med*. 2006;119:267-274

HAE is an Autosomal Dominant Disease



Frank, MM et al, Annals Int. Med 84:580, 1976

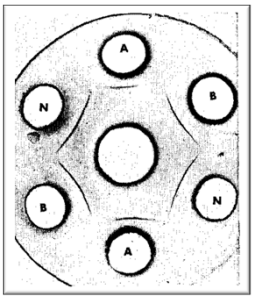
HAE Patients are Deficient in C1INH Function

Levels of Serum Inhibitor of C1-INH Activity in HAE

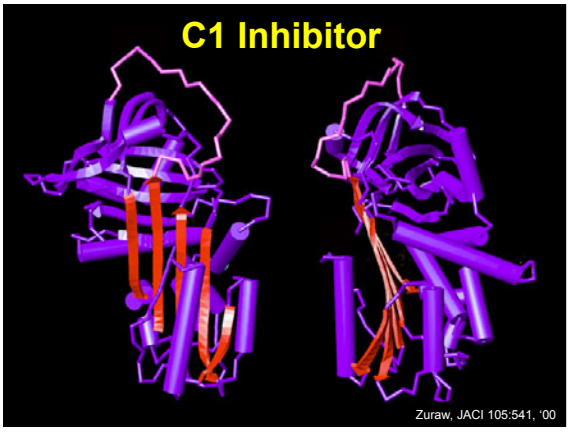
Source of Serum	#	C1-INH
Normal subjects	165	5.8 ± 1.8
Pts with HAE	12	0
Unaffected relatives	19	7.7 ± 1.4
Other angioedema	15	9.2 ± 2.6

Donaldson VH, Am. J. Med. 1963;35:37

Hereditary Angioedema
Two Genetic Variants

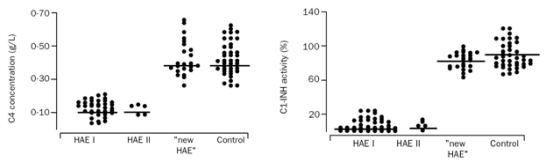


Rosen FS, Science 1965;148:957-8



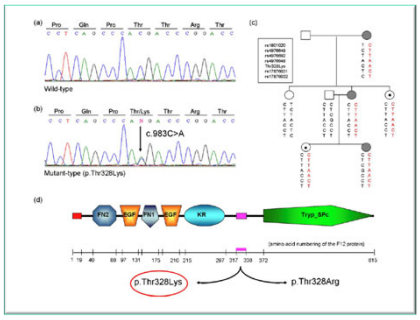
New Hereditary Angioedema: Type III

C4 level C1INH function



Bork, Lancet 2000

Factor XII Mutations in Type III HAE

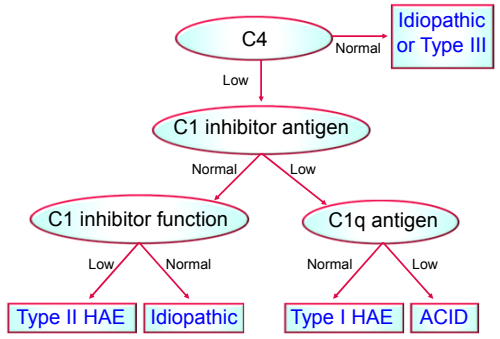


Nagy N, J Derm Sci 56:62, '09

Complement Profile in Recurrent Angioedema

	C4 Level	C1-INH Level	C1-INH Function	C3 Level	C1q Level
HAE type I	**Low**	**Low**	**Low**	**Normal**	**Normal**
HAE type II	**Low**	**Normal**	**Low**	**Normal**	**Normal**
HAE type III	**Normal**	**Normal**	**Normal**	**Normal**	**Normal**
Acquired C1INH defic.	*Low*	*Low*	*Low*	*Normal/ Low*	*Low*
ACE inhibitor	*Normal*	*Normal*	*Normal*	*Normal*	*Normal*
Idiopathic AE	*Normal*	*Normal*	*Normal*	*Normal*	*Normal*

Diagnostic Algorithm for Angioedema



Potential Errors in Diagnosis of Type III

- ***Possible false positive***
  - Idiopathic angioedema, especially non-histaminergic, may also be difficult to treat
  - Other forms of angioedema may be hormonally effected
- ***Possible false negative***
  - Not all pts are women, and not all women have a history of estrogen exacerbation
  - Only a relatively small minority of type III patients have a FXII mutation

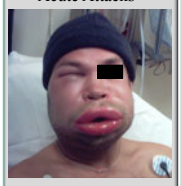
Current Status of Diagnosis of Type III HAE

- ***Required***
  - Recurrent angioedema, not responsive to CS/AH/epi
  - Strong family history, but penetrance highly variable
  - C4, C1INH antigen and C1INH function all normal
- ***Suggestive***
  - More likely to affect females, but males affected as well
  - Evidence of non-symptomatic obligate carriers
  - May be estrogen-dependent or assoc with FXII mutation
  - Age of onset tends to be later, mean age 26.8 years
  - Swelling more likely to involve face and extremities

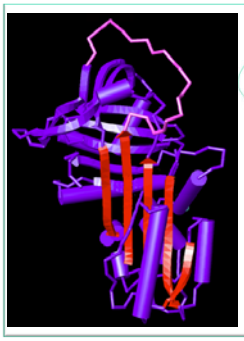
HAE Therapy

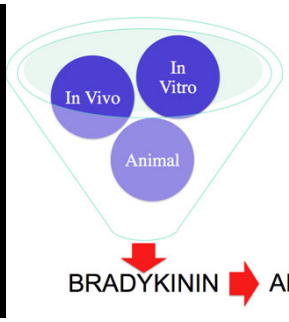
- **On-demand treatment of acute attacks**
  - To abort an ongoing attack of angioedema such that it does not progress
  - To prevent an angioedema attack from disrupting daily activities
- **Prophylactic treatment**
  - Short-term prophylaxis: to prevent an expected attack
  - Long-term prophylaxis: to minimize the frequency and severity of recurrent attacks

Pre-2008 Treatment of HAE

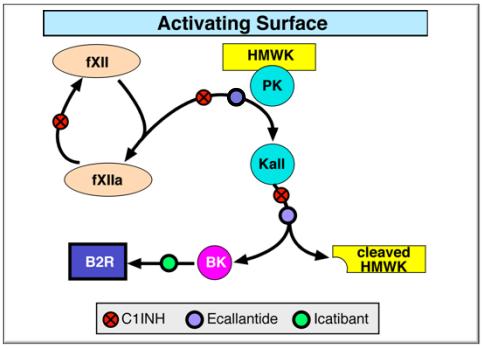
Treatment of Acute Attacks	Long-Term Prophylaxis	Short-Term Prophylaxis
		
Nothing FFP (?)	Anabolic Androgens Antifibrinolytics	FFP Anabolic Androgens

Revolution in Approach to HAE





Therapeutic Implications of Bradykinin Theory



Zuraw, Med Clinics of N. America 30(Suppl 1):58, 2011

Changing Goals of HAE Therapy

- No longer merely to keep the patient alive and out of the hospital
- Treatment should now aim to maximize patient health by:
  - Aborting acute attacks to prevent M&M
  - Minimizing significant side effects
  - Avoid disruption of normal life, esp. school, job, sleep

Hereditary Angioedema
With C1 Inhibitor Deficiency
Clinical Trials and Evidence Based Treatment

Palazzo Feltrinelli
Gargnano del Garda (Brescia) - Italy
26-29 September 2010

International HAE Conference Consensus

- All HAE patients should have on-demand treatment available
  - Patients should be trained for self administration
  - Attacks at all locations are eligible for treatment
  - Attacks should be treated as soon as they are recognized
  - Hospitalize for progressing laryngeal involvement
- Long-term prophylaxis
  - Consider when optimized on-demand therapy fails
  - Androgens are contraindicated in patients who are:
    - ≤16 y/o
    - pregnant/breastfeeding
    - do not tolerate or accept androgens

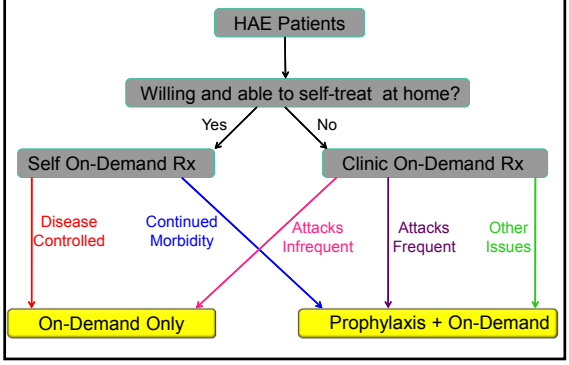
HAEA Medical Advisory Board Guidelines

- Pts should have an individualized defined management plan in place and have ready access to their health care providers
- **Treatment of angioedema attacks**
  - Must have access to at least one specific effective on-demand drug
  - On-demand treatment may be most effective when administered early
  - All attacks, irrespective of location, should be considered for treatment
  - Patients with laryngeal, tongue or throat swelling should seek emergency medical care as soon as possible

HAEA Medical Advisory Board Guidelines

- **Prophylactic treatment**
  - Long-term prophylaxis is appropriate for pts who do not achieve sufficient benefit from on-demand therapy
  - Androgens should not be used if the pt does not tolerate them, in pts under the age of 16, or in pregnant/breastfeeding women. In addition, caution should be exercised if the dose exceeds danazol 200 mg/day
  - Pts on prophylaxis still require on-demand therapy be available
  - Prophylaxis should be used at the lowest effective dose that controls disease activity

A Proposal for Managing HAE Patients



Conclusions

- HAE is an uncommon but serious disease
  - Key to minimizing morbidity and mortality is early recognition
  - Type I and II HAE results from C1INH mutations, Dx is easy
  - Cause of Type III HAE remains uncertain; dx difficult
- Pre-2008 treatments were variably effective but clearly suboptimal
- Important novel therapies have been developed and consensus opinion about treatment strategies have emerged:
  - All patients with Type I/II HAE should have access to effective on-demand medications with a well delineated treatment plan
  - Prophylaxis is best reserved for patients in whom on-demand treatment is not sufficiently effective
  - The physician must minimize treatment side effects
  - Therapy needs to be tailored to individual needs of the pt